Blood Substitutes

Baxter Healthcare Corporation
Route 120 & Wilson Road
Round Lake, Illinois 60073-0490

847.270.5300
Fax: 847.270.5306

Baxter

July 1, 1997

7450 '97 JUL -3 P1:27

Docket Number 95S-0158
Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Dr. rm. 1-23
Rockville, MD 20857

RE: Investigational New Drug Application #6859

Dear Sir/Madam:

In accordance with 21 CFR §312.54 we are enclosing a copy of the information that has been publicly disclosed by the Institutional Review Board (IRB) at Vanderbilt University Medical Center, Nashville, TN, concerning research involving an exception to informed consent. This includes the agenda (Attachment 1, presented by the principal investigator, and Attachment 2, presented by the Chairman of the IRB) and minutes (Attachment 3) from the Community Committee Meeting on March 24, 1997; minutes from the Human Relations Commission Meeting on April 7, 1997 (Attachment 4), the Davidson County Delegation Meeting on April 21, 1997 (Attachment 5), and the Davidson/Williamson County Chapter of Mothers Against Drunk Driving (MADD) Meeting on April 22, 1997 (Attachment 6); a news release (Attachment 7) and a one-page summary of the newly enacted federal regulation regarding emergency research and waiver of informed consent (Attachment 8) that was sent to the Rural Hospital Association by the IRB for dissemination to the rural hospitals and their community boards, along with the cover letters accompanying the release (Attachment 9, 10); an article that appeared in the local paper, the Nashville Tennessean, on April 22, 1997 (Attachment 11); an article that appeared in the local paper, The Tennessean, on April 23, 1997 (Attachment 12); an article that appeared in a local paper, the Nashville Business Journal, on April 28, 1997 (Attachment 13); two internal news releases (Attachment 14, 15) and resulting articles that appeared in the hospital newspaper, VUMC Reporter, on March 14, 1997 (Attachment 16) and April 25, 1997 (Attachment 17); and an article that appeared in a local newspaper, The Tennessean, on April 30, 1997 (Attachment 18). In accordance with 21 CFR §312.54, this information is also being submitted to the Docket Number 95S-0158 in the Dockets Management Branch. In accordance with 21 CFR §312.54, this information is also being submitted to the IND file.

Based on information received from the clinical site, the investigator and IRB achieved

95S-0158

SUP4

community consultation by presenting a proposal of the study to the Community Committee (Attachment 1, 2, 3). Based on the recommendations of the Community Committee, the proposed research study was presented at various other community meetings (Attachments 4, 5, 6). Additionally, a news release and a one-page summary of the newly enacted federal regulation regarding emergency research and waiver of informed consent was sent to the Rural Hospital Association for dissemination to the rural hospitals and their community boards (Attachment 7, 8).

If there are any questions concerning this information, please contact me at (847)270-5313.

Sincerely,

Maulik Nanavaty, Ph.D.
Director Regulatory Affairs
Blood Substitutes Program

high," he said.

The new synthetic blood product has a shelf life of more than a year, and can be thawed for use after it is frozen.

"All you'd have to do is manufacture it, ship it over on one airplane and thaw it when you need it," Morris said. "If this product is proven to work, it may have tremendous implications for the military not far down the road."

Morris said it is believed that the earlier the synthetic blood product is used the better it may work. If the product is proven effective, it will more than likely be of best use before the patients actually get to the hospital, administered while they are en route, either in a ground or air ambulance.

"The next step will be to get this product into the pre-hospital environment," Morris said.

For now, the question of whether the product works better than saline is all that this project attempts to answer.

"It's not a question of whether this product serves as a boxcar. We know it does. It's not a question of whether it's safe. It has been demonstrated to be safe. The question is can we give it, can we give it early enough and can we give it in volumes sufficient enough to save lives," Morris said.

"We're confident we're not going to make anyone worse. The question is can we make a significant number of people better."

As part of the new regulations giving research institutions the authority to treat gravely ill patients with investigational drugs or devices in some emergency situations without their consent, VUMC is seeking feedback from the community. To respond, please contact Vanderbilt's Institutional Review Board at (615) 322-2918 or fax comments to (615) 343-2648.

VUMC

Attachment 1

DIASPIRIN CROSS LINKED HEMOGLOBIN

WHAT IS IT?

- ***Blood substitute***
  - carries oxygen to the tissue
  - Differentiate from saline

WHERE DOES IT COME FROM ?

- ***Expired Human Blood***
- ***Pasteurized***
  - Reduced Risk Of Viral Transmission

WHY DO WE NEED IT?

- ***Trauma as a Disease***
  - 150,000 deaths In USA/Yr
  - 300,000 disabilities
  - Trauma Demographics
- ***Issues with Human Blood Transfusion***
  - Specific Blood Types
  - Storage Issues
  - Disease Transmission
- ***Attributes of DCLHb***
  - Universal Donor
  - Storage Issues
  - Disease Transmission

IS IT SAFE?

- ***Studied in patients for 4 years***
  - Cleared by the FDA
- ***Reviewed by > 25 IRBs***
  - 800 patients

IS IT EFFECTIVE?

- ***The Elective Environment***
  - High Blood Loss Surgery
  - Open Heart Surgery
  - Hemodialysis Study
  - Hip Surgery
- ***The Emergency Environment***
  - We Don't Know

WHAT DO WE PROPOSE TO DO?

- ***Look At A Group of Severely Injured Patients***
  - In Shock
  - With 40% Mortality
- ***The Purpose***
  - To Stabilize shock
  - To improve Patient Outcome
- ***Randomization***

divide into 2 Groups

The Endpoints

Decreased Death Rate

Decreased Complication Rate

WHY DO WE NEED WAIVER OF CONSENT

Consent will Be Obtained If Possible

Most Likely from the Family

Patients are very sick

40% predicted mortality

Must intervene early

concept of physiologic reserve

Future Studies

Prehospital

SUMMARY

Diaspirin cross linked Hemoglobin is a :

Blood Substitute

It is safe

It is effective in elective surgery.....

And Now The time has come to find out if it is effective in the emergency environment.

Attachment 2

EMERGENCY RESEARCH AND WAIVER OF CONSENT

WHAT: On October 2, 1996, the U.S. Food and Drug Administration (FDA) and the Department of Health and Human Services (HHS) issued a new regulation giving medical center Institutional Review Boards (IRB) the authority to waive informed consent requirements in some very specific emergency room/acute care clinical investigations. The new regulation applies to a limited class of research activities involving human subjects who are in need of emergency medical intervention, but who are unable to give informed consent, have a life-threatening medical condition and who do not have a legally authorized person to represent them.

The intent of the new regulation is to allow research in life-threatening conditions for which available treatments are unproven or unsatisfactory and where it is not possible to obtain informed consent, while establishing additional protections to provide for safe and ethical studies. The new regulation went into effect November 1, 1996.

COMMUNITY CONSULTATION: The FDA and HHS recognize that subjects with life-threatening conditions who can neither give informed consent nor refuse enrollment are in a vulnerable position and are in need of additional protective measures to ensure their safety and welfare. The new regulation requires that additional measures be taken by the medical center IRB when reviewing, approving, and monitoring research. The IRB will review a specific research protocol, seek community consultation, and then take into consideration the community response to approve or disapprove the research protoool.

PROPOSED PROTOCOL: The purpose of this research study is to determine the effect of DCLHb (Diaspirin Cross-Linked Hemoglobin) in the treatment or prevention of the harmful effects of blood loss in severely injured trauma patients. The death rate in these patients may be as high as 40% despite receiving the best medical treatment available. Patients who have experienced a severe traumatic injury often suffer from shock due to excessive blood loss. Shock cannot always be treated by current medical therapies. DCLHb is a purified human hemoglobin solution. DCLHb carries oxygen and may improve oxygen delivery to vital organs, reversing the effects of shock, and may allow for increased survival and complete recovery of more patients who are severely injured.

The purpose of this research study is to determine how well the new hemoglobin solution works in treating or preventing the harmful effects of blood loss due to severe injury. Nationwide, approximately 850 patients will take part in this study at 40 trauma centers. Approximately 40 patients will take part at Vanderbilt Medical Center.

Costs of the research will be covered by Baxter International. DCLHb is currently approved in research with non-trauma patients who are able to provide consent.

Attachment 3

Minutes -Community Committee
March 24, 1997

Present: Lois Wagner, David Sewell, Ellis, Donald Blanton, Rubel Shelly, Jan VanEys, Barbara Clinton, Terry Kopansky, Barbara Murphy, Betty Nixon, Leona Marx, Henrietta McCallister, Marilyn Yager, Virginia Wiley, Carolyn Hall

Guests: Judy Jenkins, MSN, RN, John Morris, MD

1. Reviewed minutes and discussed meeting time and date. Next meeting scheduled for April 14, 1997 at 12:00noon. The meeting room to be announced at a later time.

2. Dr. John Morris presented proposed research,"The Efficacy Trial of Diaspirin Cross-Linked Hemoglobin (DCLHb™) in the Treatment of Severe Traumatic Hemorrhagic Shock", (Baxter Healthcare Corporation), to the committee.

3. Rev. Shelly raised issues regarding the risks associated with Diaspirin.

4. Dr. VanEys raised the issue regarding costs related to the study and whether or not Baxter was financially liable for those costs. A question whether the community should be made aware of costs issues was discussed and it was determined that this information should be disseminated to the community in future presentations. The Committee emphasized the need to address the issue that healthcare must be effective and cost-effective when presenting this information to the community-at-large.

5. Discussion followed about the demographics and the study population. Dr. Morris stated that statistically males 18-35 years of age are a typical population seen in trauma centers.

6. Ms. Nixon raised the issue that this study may potentially prolong life for a population who may have poor outcomes. Dr. Morris stated that 2/3 of previous studied populations were back to work within a year, thus indicating a potential benefit from treatment.

7. Ms. Marx clarified the purpose of the data monitoring board requirement of the committee.

8. Dr. Murphy asked for concerns that the community members may have regarding this study. Dr. VanEys raised the concern of the waiver of consent in research but did not feel that should prevent the proposed research from being presented to other community groups.

9. Discussion about prospective groups to target for community notification and the difficulties in reaching the rural sections of the area served by the Vanderbilt University Trauma Center followed.

10. Ms. Marx reiterated the purpose of the research and emphasized the fact that these are subjects who have poor outcomes whether or not the subjects are participants in the study.

11. The following recommendations were made regarding prospective groups to target:
    - MADD (Mothers Against Drunk Driving)
    - Citizen Boards of the Rural Hospital Association
    - Metro Human Relations Commission
    - Local and rural newspapers - press releases and articles
    - College newspapers - Vanderbilt University and Tennessee State University
    - Nashville Delegation of the Tennessee Legislature

12. A brief discussion about a response time for community feedback would be determined following the presentations for Dr. Morris' proposed research and be discussed at the next meeting.

13. Issues involving community education and long-term meeting schedule deferred tot he next meeting.

Attachment 4

April 7, 1997

Nashville Metro Human Relations Committee
222 2nd Avenue North
Nashville, TN

5:15- 5:25 PM

Attendees: Betty Nixon, Marilyn Yeager, Judy Jenkins, R.N., M.S.N., John Morris, Jr., M.D. and Virginia Wiley

Betty Nixon introduced the group. A brief overview about the newly enacted regulation about emergency research and waiver of consent was presented by Virginia Wiley. Dr. John Morris presented an overview of his proposed research including information about the purpose, the risks and benefits and contact information for questions or comments.

The Committee members had questions about the source of the solution and its administration. There was one question regarding the study design. The Committee members were supportive of the research and expressed no concerns or indications to prevent the study from going forward.

Virginia Wiley, R.N.
Director, IRB

VW

April 21, 1997
Davidson County Delegation Meeting
2:00pm

Presentation of IRB # 8618 - The Efficacy Trial of Diaspirin Cross Linked Hemoglobin (DCLHb™) in the Treatment of Severe Traumatic Hemorrhagic Shock (Baxter Healthcare Corporation) by Dr. John Morris, Jr. To the Davidson County Delegation Meeting on 4/21/97 in Room 30 of the Legislative Plaza.

Betty Nixon gave a brief introduction to the purpose of attending the meeting and introducing the speakers Dr. John Morris, Jr. and Virginia Wiley. Virginia Wiley presented a short summary of the new emergency research and waiver of consent regulation. Dr. Morris presented a brief overview of his research study to include information about the purpose, the risks and benefits and contact information if individuals had comments or questions.

Questions from the Delegation members dealt with issues about the solution which were answered by Dr. Morris. There were no additional comments.

Virginia Wiley VW

Attachment 6

April 22, 1997

MADD Meeting @ Hillsboro Presbyterian Church, 7:30pm

IRB # 8618, The Efficacy Trial of Diaspirin Cross-Linked Hemoglobin (DCLHb™) in the Treatment of Severe Traumatic Hemorrhagic Shock (THS 95.1)

Comments of participants at meeting to inform community of proposed research.

1. Raised questions about side effects to the investigational product. Clarifying that the side effects and what the worse possible side effects.
2. Questioned the source of the DCLHb.
3. Is the participation voluntary and may the subject withdraw.
4. Asked for clarification of the order of consent or informing of subject's family members.
5. Raised question whether or not participation in the study would affect organ donation options and/or procedures.
6. Raised question if a toxicology screen would be masked or altered by the investigational product.
7. Raised question if the this investigational product would artificially lower blood alcohol level.
8. Raised question as to whether or not this investigational product could have long-term benefits to comatose subjects.
9. Reviewed inclusion criteria following several references to personal experiences of the audience.

Attachment 7

VANDERBILT MEDICAL NEWS

Vanderbilt University

OFFICE OF NEWS
AND PUBLIC AFFAIRS
MEDICAL CENTER
CCC-3312
1161 21st Avenue South
Nashville, TN 37232-2390
(615) 322-4747

contact: VUMC Office of News and Public Affairs **phone (615) 322-4747**

VANDERBILT TO TEST SYNTHETIC BLOOD PRODUCT

Vanderbilt University Medical Center's trauma center is gearing up to test a new synthetic blood product on severely injured patients.

The new investigational product will be administered to patients who are in shock due to excessive blood loss. VUMC is one of 35 health care centers across the country testing the new product to determine if it is a viable alternative to saline infusion, the standard treatment.

The upcoming trial falls under recently adopted federal regulations giving research institutions the authority to treat gravely ill patients with investigational drugs or devices in some emergency situations without their consent (see VUMC Reporter, March 14).

The synthetic blood product, called Diaspirin Cross-Linked Hemoglobin (DCLHb), is a purified human hemoglobin solution. Hemoglobin is the protein in red blood cells that carries oxygen. The synthetic blood product, which has already been proven safe in prior studies, is prepared from units of human red blood cells from volunteer donors who have been tested negative for the viruses that cause hepatitis and AIDS. Unlike blood, it does not need to be cross-matched and is easily stored in the emergency department so that it is available as soon as the patient arrives.

The multi-center study will compare the use of the synthetic blood product to saline, the current standard of treatment when blood is not readily available.

"This study is designed to try to identify the very sickest people who can benefit from the administration of a blood substitute when blood is not available," said Dr. John A. Morris Jr., professor of Surgery, and the principal investigator of the Vanderbilt portion of the study. Also participating in the study will be Judy Jenkins, R.N., M.S.N., clinical nurse specialist and case manager in the division of Trauma.

Before blood can be given to a patient, the patient must be cross-matched so that the correct type of blood is given, Morris explained. Giving a patient the wrong type blood can be a "fatal

mistake," Morris said.

Cross-matching can take up to 45 minutes, time that is not available when an injured patient is in shock, he said.

When a patient is in shock the body is unable to deliver enough blood and oxygen to all of the vital organs and tissues, Morris explained. Because of this, the vital organs may no longer be able to function and the patient may die. About 150,000 people die each year due to trauma injuries.

"The ravages of shock are dependent upon two things — the magnitude of the injury and the length of time before the patient gets therapy for that injury," Morris said. "The most important therapy we can give people is the ability to get oxygen to the tissues," Morris said.

A breathing tube can deliver oxygen from the air to the blood, Morris said. But within the blood there has to be a method by which oxygen is carried to the tissues. That is the importance of hemoglobin.

"In a normal situation, the boxcar that delivers oxygen is called hemoglobin," Morris explained. "Hemoglobin is the business end of what a blood transfusion is all about."

But blood transfusions take time to prepare.

"If we had something to give patients in the first 45 minutes that would carry oxygen, i.e. a boxcar, we could shorten the time they are without enough oxygen to the tissues. And that's good," Morris said.

Currently, when it is not feasible to wait for blood to be given, the treatment of choice is the rapid infusion of large volumes of saline to replace fluid loss due to injury, followed by the transfusion of blood to replace the fluid and blood loss.

The nationwide study will involve approximately 850 severely injured patients at the 35 trauma centers. About 20 to 30 patients will be involved at each institution.

Only those at the greatest risk of death can be considered for the study. Patients can be either male or female and must be at least 18. Patients with severe head injuries or whose heart has stopped in the hospital will not be entered into the study.

The study participants will be randomized. Some will receive the new synthetic blood product. Some will receive an equal amount of saline. All will receive standard therapies in addition to the investigational product. The order of assignment will be determined before the patients are entered into the study so neither the patients nor the patients' physician can choose which solution is given. Possible risks associated with the synthetic blood product include a temporary yellowing of the skin, red discoloration of the urine that does not affect kidney function, abdominal cramps and an increase in blood pressure, a desired effect in a patient suffering from shock.

Morris said the implications of the study are important for several reasons.

"It's important to the people of Tennessee for several reasons. This is a rural state and the transport time to definitive care is relatively long. Consequently the risks of shock are relatively

Attachment 8

Emergency Research and Waiver of Consent
[FDA 21 Part 50.24, DHHS 45 CFR Part 46.498]

On October 2, 1996, (Federal Register, Vol. 61, No. 192, pp. 51498-51535), the Food and Drug Administration (FDA) and the Department of Health and Human Services (DHHS) issued a new regulation giving Institutional Review Boards the authority to waive informed consent requirements in some acute care clinical investigations. The new regulation applies to a limited class of research activities involving human subjects who are in need of emergency medical intervention, but who are unable to give informed consent and have a life-threatening medical condition and who do not have a legally authorized person to represent them. The intent of the new regulation is to allow research on life-threatening conditions for which available treatments are unproven or unsatisfactory and where it is not possible to obtain informed consent, while establishing additional protections to provide for safe and ethical studies. The new regulation went into effect November 1, 1996.

The FDA and DHHS recognize that subjects with life-threatening conditions who can neither give informed consent nor refuse enrollment are in a vulnerable position and are in need of additional protective measures to ensure their safety and welfare. The new regulation requires additional protective measures be taken by the IRB when reviewing, approving and monitoring research conduct.

The regulation requires that the IRB must find and document the following;

- The research involves a life-threatening situation and available treatment is either unproven or unsatisfactory
- Obtaining consent is not feasible
- The research is of potential direct benefit to the subject
- The research cannot be practically carried out without waiver of consent
- Consultation with representatives from the communities from which the subjects are likely to come
- There must be public disclosure to the community of the risks and of the benefits and purpose of the study prior to initiation
- At completion of the study, there be public disclosure of the demographics of the study population and the results
- Additional reporting and recordkeeping requirements with respect to FDA drug and device applications must be met, and the sponsor must establish an independent data monitoring committee

Attachment 9

Vanderbilt University Medical Center

Vice-Chancellor for Health Affairs - Institutional Review Board

CCC-3322 Medical Center North
Nashville, TN 37232-2103
(615) 322-2918 Fax: (615) 343-2447
E-mail: irb@mcmail.vanderbilt.edu

May 23, 1997

Susan Veale
Rural Hospital Association
5 th Floor, Cordell Hull Building
Nashville, TN 37219

RE: News Release to be Distributed to the Rural Hospital Association

Dear Ms. Veale:

Thank you for your patience. I apologize for the delay in sending the information. Attached please find a copy of the news release that Betty Nixon and I have spoken with you about. We would like to distribute the news release and the one-page summary about the newly enacted federal regulation regarding emergency research and waiver of consent to the rural hospitals served by the Vanderbilt University Trauma Center to solicit feed back from the community about the study in the news release. The new regulation requires that the communities from which subjects may come, be informed about the purpose, the risks and the benefits of the proposed research, and feedback from the community sought before the research may be initiated.

The distribution to the rural hospital association is a part of the community awareness requirement for the study in the news release which is currently in the process of being reviewed by the Institutional Review Board office at Vanderbilt. Responses regarding this proposal may be directed to the Institutional Review Board Office at Vanderbilt.

Institutional Review Board
Vanderbilt University
CCC 3322, Medical Center North
Nashville, TN 37232-2103

(615)322-2918
fax (615)343-2648
(email) irb@mcmail.vanderbilt.edu

If you have questions, please feel free to contact me at 322-2918. Thank you for your assistance with this matter.

With best regards, I am

Sincerely,

Virginia Wiley, R.N.
Director, Institutional Review Board

/vfw

cc: Betty Nixon
Marilyn Yager
John A. Morris, Jr., M.D.

Attachments

Vanderbilt University Medical Center

Vice-Chancellor for Health Affairs - Institutional Review Board

CCC-3322 Medical Center North
Nashville, TN 37232-2103
(615) 322-2918 Fax (615) 343-2447
E-mail: irb@mcmail.vanderbilt.edu

May 23, 1997

To Whom It May Concern:

Attached please find a one page summary of newly enacted federal regulations regarding emergency research and waiver of consent and a news release about a proposed research study which falls within this narrow category of research.

The new regulation which was issued by the Food and Drug Administration (FDA) and the Department of Health and Human Services (DHHS) gives Institutional Review Boards (IRB's) the authority to waive informed consent requirements in some acute care clinical investigations. This new regulation applies to a limited class of research activities involving human subjects who are in need of emergency medical intervention, but who are unable to give informed consent and have a life-threatening medical condition and do not have a legally authorized representative to represent them. The intent of the new regulation is to allow research on life-threatening conditions for which available treatment are unproven or unsatisfactory and where it is not possible to obtain informed consent.

The FDA and the DHHS recognize that subjects with life-threatening conditions who can neither give informed consent not refuse treatment are in a vulnerable position and are in need of additional protective measures to ensure their safety and welfare. One of theses measures is to have IRB's seek feedback from the community-at-large about proposed research before it is initiated.

On behalf of the principal investigator, Dr. John A. Morris, Jr., M.D., of the research study currently under review and the Institutional Review Board at Vanderbilt University, we would like to request that the attached news release and summary of the regulation be disseminated to your hospital staffs and community boards for their feedback. Responses from the community can be directed to the Institutional Review Board Office at Vanderbilt University at the following address:

Institutional Review Board
Vanderbilt University
CCC 3322, Medical Center North
Nashville, TN 373232-2103

(615)322-2918
Fax (615)343-2648
(email) irb@mcmail.vanderbilt.edu

Thank you for assistance with this matter. If you have questions or concerns, please feel free to contact the Institutional Review Board Office.

Sincerely,

Virginia Wiley, R.N.
Director, Institutional Review Board

/vfw

cc: John A. Morris, Jr., M.D.

Attachments

Attachment 11

Experiments to start on critically wounded

Vanderbilt researching substitutes for blood

HEALTH CARE

By DUREN CHEEK
Staff Writer

Some critically injured gunshot and traffic accident victims brought to Vanderbilt University Medical Center will be used in a research project without their consent.

The plans were outlined yesterday to the Davidson County state legislative delegation by Dr. John A. Morris Jr., professor of surgery.

The Food and Drug Administration and the Department of Health and Human Services announced regulations last fall that give medical centers authority to waive informed consent in some emergencies. Normally, a patient, relative or guardian would have to consent to the experimental procedure.

Virginia Wiley, director of Vanderbilt's Institutional Review Board, said the Vanderbilt program is expected to begin within two or three weeks, or as soon as Vanderbilt informs the community about the purpose, risk and benefit of the research. Yesterday's presentation was part of that effort.

The research will determine how well a new hemoglobin solution made by Baxter International pharmaceutical works in treating or preventing the effects of blood loss.

"In its simpliest terms, it is a substitute for blood," Morris said. "Hemoglobin is the molecule in blood that carries oxygen, and oxygen is absolutely essential for tissues and organs to function properly."

About 850 patients will be involved in the study nationwide, including as many as 40 at Vanderbilt.

"I think about 80% will be victims of traffic crashes and about 20% will be victims of penetrating injuries, gunshots or stab wounds," Morris said.

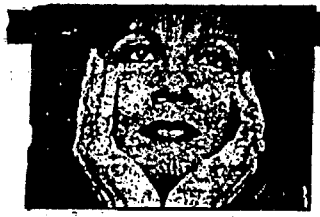
Morris said the solution has been "clearly effective" in elective surgery and has minor side effects, including raising blood pressure, yellowing of the body and turning urine red.

The new federal regulation gives hospital review boards authority to waive the necessity of consent if the patient is in need of emergency medical intervention or has a life-threatening medical condition.

Morris said the death rate among severely injured trauma patients may be as high as 40% because they often suffer from shock due to excessive blood loss.

The purified human hemoglobin solution to be used in the study carries oxygen. That may improve oxygen delivery to vital organs, reverse the effects of shock and may allow for increased survival of the severely traumatized patient, he said. ■

Attachment 12



LIVING, 1D

CMA's 'precursor' to hand out awards

Loveless among ACM nominees

WEDNESDAY
APRIL 23, 1997

TODAY'S HIGH 57° TONIGHT'S LOW 40°

Complete weather forecast on 10B

SPORTS, 1C

Arena concession: We'll make it right

Food stand mix-up worked out

NASHVILLE, TENNESSEE

THE TENNESSEAN

A GANNETT NEWSPAPER

VOLUME 93, NO. 113 • 5 SECTIONS • 3

SECOND CLASS POSTAGE PAID IN NASHVILLE, TN

Consent issue spurs ethics debate on medical procedure

By TAMMIE SMITH
Staff Writer

HEALTH CARE

It's a new medical treatment, with the potential to save lives. But because researchers will not have to get patient consent in clinical trials, it's raising long-standing ethical questions about what's appropriate in the medical arena.

Under new U.S. Food and Drug Administration rules drafted in November, Vanderbilt University Medical Center, along with 34 other medical centers nationally, will test a blood substitute called HemAssist on victims of car accidents and other traumas brought to emergency rooms in critical condition.

But across the country, some have criticized the public notification rules as too vague, and question whether the research will rely too heavily on certain groups and whether it's the start of a trend toward easing patient notification rules.

"We always hear about going down the slippery slope," said Dr. Louis J. Bernard, a cancer specialist and acting director of Tennessee Health Decisions, a group concerned with medical ethics.

"But it's my impression that in 1997 in America that is not likely to happen. It happened in the past, with the Tuskegee incident. I think this country has been sufficiently sensitized in the last 15-20 years, and that's not likely to occur again."

The Tuskegee reference is to experiments starting in the 1930s in which black men in Alabama were unwitting subjects of medical research. The men had syphilis and were intentionally left untreated to study the disease's progress.

As a result of that incident and others, the government strengthened rules for involving humans in medical tests. In almost every case, patients must be told of the pros and cons of research in detail before participating.

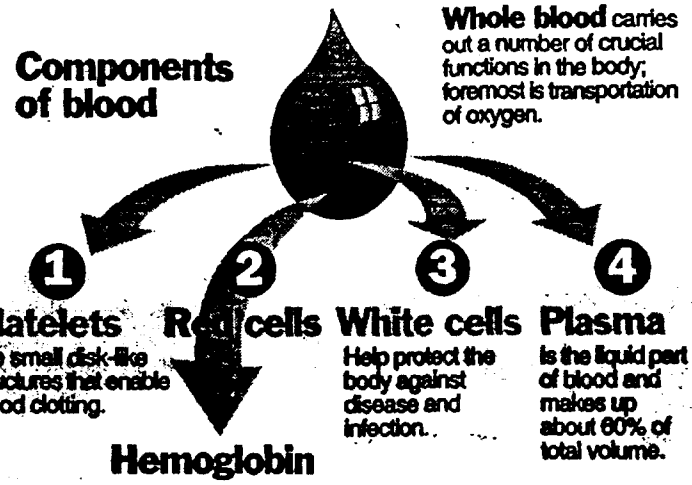
But that requirement has created a dilemma for emergency medicine, where lives can be saved or lost in a matter of minutes if treatments are not given quickly, says trauma surgeon Dr. John A. Morris Jr., who will oversee Vanderbilt's HemAssist study. Advances in emergency medicine have been stymied in the last decade by the inability to get informed consent from critically injured patients.

"The reason the FDA promulgated these guidelines is if we are going to make progress in dealing

◊ Turn to PAGE 2A, Column 1

Breaking down blood

HemAssist is considered a hemoglobin therapeutic, which acts like hemoglobin, a derivative of whole blood. These therapeutics are proving to be valuable blood substitutes. Here's a look at the properties of hemoglobin and how it relates with other blood elements.



SOURCE: Baxter International Inc., World Book Enclopedia JIM CHAPMAN / STAFF

Procedure raises ethics debate

FROM PAGE 1A

with severely injured patients or heart attack patients, it's critical to get intervention to those patients early," he said.

"Unless we have community agreement that we can do science in an unbiased fashion, under this very specific waiver of consent rules, we will never be able to make progress in terms of the 150,000 people who die a year from trauma or in those people who have massive heart attacks."

Vanderbilt expects to enroll 40 patients in the study, a fraction of the 850 involved nationwide. Half will get traditional treatment, half traditional treatment plus HemAssist. No one, Morris says, will be denied the most appropriate treatment.

"When you have a big injury and you bleed, the standard treatment is to initially replace that blood lost with salt water," Morris explained.

"But the problem is while that salt water helps to maintain some degree of oxygen flow, it does not carry oxygen but frees up blood cells that are hidden in other tissues. HemAssist carries oxygen almost as well as red blood cells."

HemAssist is made by Baxter HealthCare Corp. of Deerfield, Ill. It is the the first blood substitute to reach Phase III FDA trials, according to the company. Its effectiveness has already been tested in more than 700 people, including healthy volunteers.

Only the sickest trauma patients — those whose lives depend on getting blood transfusions as quickly as possible — will be included in the research. And even after patients get HemAssist, efforts for consent will continue. Once informed, they or their representative have the option to withdraw.

The FDA rules require medical centers doing research under the new guidelines to let the community know and solicit input. Vanderbilt has done that through presentations to the Metro Human Relations Commission, state legislators and just last night, a Mothers Against Drunk Driving group.

"There are no easy answers to a lot of the questions that will be raised," said Dr. Richard Zaner, a Vanderbilt expert on medical ethics.

"This was the end product of a very long process to see if there is a way to do for people who are subjects of traumatic accidents what we can do for other people — to do research to keep improving the way we treat them." ■

Attachment 13

Capsules

The Business Week in Review

Gresham Smith gets project, Washburn cans plant

Dollar General Corporation has named Nashville-based Gresham Smith and Partners as its architectural and engineering firm for its new corporate headquarters in Goodlettsville. The project is estimated to cost $35 million on a 39-acre site between Conference Drive and Interstate 65. Groundbreaking is expected to take place in the fall, and occupancy is expected to occur in late 1998. More than 300 corporate employees will work there.

•

The Aerostructures Corp., of Nashville, a manufacturer of airplane components, has been merged with Boca, Calif.-based Contour Aerospace.

The move is a corporate realignment on the part of the Washington, D.C.-based The Carlyle Group. The investment partnership bought both aircraft companies last fall and had considered combining them ever since, as they were essentially competing against each other.

The merged companies combined will employ about 2,000 workers and have annual sales of around $300 million.

•

Washburn International, the Vernon, Ill.-based guitar manufacturer, has canceled its plans to open a plant and new company headquarters in Mount Juliet.

The company did not cite a reason for its decision and the halting of construction for the plant which already stands partially built in an industrial park next to Interstate 40. The plant was expected to eventually employ up to 500 people.

Washburn has put the site up for sale and is asking $1.7 million for the 84,000-square-foot building and the 15-acre lot on which it stands. Whoever purchases the property will have to pay $250,000 to the Mount Juliet-Wilson County Development Board, which trimmed $250,000 off the original price of the property to entice the company to locate there.

•

Vanderbilt University Medical Center is planning to test experimental treatment of severe trauma patients to test the effectiveness of HemAssist, a new blood substitute developed by Baxter International Pharmaceutical. The hemoglobin solution which is designed to carry oxygen to tissues and organs will be used in some cases without consent of the critically injured patients receiving the experimental solution.

The Food and Drug Administration and the Department of Health and Human Services last fall gave medical centers the authority to waive informed consent in some emergencies where there is no time to be wasted obtaining it. Experimental procedures normally require the consent of the patient or a relative or a guardian.

The hemoglobin solution has proved successful in elective surgeries and has only minor side effects.

The Vanderbilt program, which is expected to involve as many as 40 patients, is planned to begin in two or three weeks as a part of a nationwide effort that will involve 850 patients in 34 other medical centers.

•

Tennessee State University honored 29 students, with two receiving the James A. Hefner Award, during its second annual College of Business Academic Awards Luncheon held April 25.

The awards luncheon included local business leaders and representatives who have donated to the university's College of Business program.

The James A. Hefner Award, named for TSU's president who established the program, awarded both an undergraduate business student and graduate business student monetary gifts.

Local businesses and individuals who have contributed to the College of Business's Wall of Excellence Scholarship and Development campaign include: Aldi, American General Insurance, Arthur Anderson, BellSouth, Castner-Knott, Central Parking, Deloitte & Touche, Taylor Henry, Holland Memorial Fund, Samuel H. Howard, The Marion Ewing Kauffman Foundation, KPMG Peat Marwick, Kraft Bros. CPA, Kroger, NBD Bank, Nissan, Werthan Packaging and United Cities Gas.

•

Nashville Public Radio has purchased a site on Mainstream Drive in MetroCenter for its planned $2.6 million facility, according to General Manager Rob Gordon.

The building is being funded by tax-exempt bonds, issued by the Metro Industrial Development Board and marketed and underwritten by J.C. Bradford as well as from a building fund drive this summer in which $2.3 million will go toward the building and $235,000 for the 1.5 acre purchase.

The new 11,500-square-foot building designed by Dallas-based Russ Design Group, will have four studios, of them to be operating immediately facility is also designed to allow an additional 5,000 square feet of expansion.

Nashville Public Radio operates WPLN-FM here and WHRS-FM in Cookeville.

•

PediaNet LLC has been formed group of Nashvillians for the purpose developing after-hours pediatric clinics accommodate the medical needs of children ages 18 and under. Clayton Associates LLC has an executive management contract with the new company, which plans to begin construction on the first clinic in Brentwood this June.

Officers of the new company include John B. Crysel, currently the CEO of Middle Tennessee Hospitals in Johnson City and soon to be chief operating officer of PediaNet; John T. Netterville Jr., founder and chief medical officer; Deborah M. Clarke, chief financial officer; and Janice E. Hight, president of clinic operations. Additional directors include Fred C. Good Jr., chairman and co-CEO of Envoy Corporation; Aubrey B. Harwell Jr., a partner in Nashville law firm Neal & Harwell; Hertik; Dr. J. David Netterville; Steve McWhorter, vice president of managed care for OrthoLink Physicians Corp. co-founder of Clayton Associates; Lady Jackson, executive director of the Mayor's Office of Economic Development.

At least two additional locations are planned to open this fall in the Nashville area. After that, Crysel says PediaNet

Attachment 14

by Doug Campbell

A new federal regulation giving research institutions the authority to treat gravely ill patients with investigational drugs or devices in some emergency situations without their consent is being implemented at Vanderbilt University Medical Center.

The government's guidelines apply to a limited class of research activities — those involving persons in desparate need of possible life-saving treatment but who are unable to give consent and have no family or someone to legally represent them.

"The community-at-large must now be made aware of the specific research being proposed," said Virginia Wiley, director of VUMC's Institutional Review Board.

"It's an additional step in the approval process," she said, "but it also means some people will now have access to care they may not have had before."

The U.S. Food and Drug Administration and U.S. Department of Health and Human Services regulation will come into play when:

- subjects are in a life-threatening situation;
- available treatment is either unproven or unsatisfactory;
- obtaining consent is not feasible;
- there is potentially a direct benefit to the patient but the investigational treatment cannot be administered without waiving consent.

VUMC is currently forming a panel of Nashville community leaders to serve as a liaison between the university's Institutional Review Board and the various sectors of the city. The group will be responsible for informing their own community of the purpose, risks, benefits and results of the research.

Additional safeguards have been included in the regulation calling for specific reporting and record-keeping, an independent data monitoring committee and full disclosure of the results and demographics upon completion of the study.

Historically, approval by institutional review boards throughout the country has been a rigorous process, one that ensures that the patient's rights are protected.

"Currently, the process for reviewing emergency research protocols requires that the investigator submit a proposal with appropriate documentation to the IRB," Wiley said.

"It is reviewed by the IRB and, following satisfactory response by the investigator to the concerns and issues raised by the committee, final approval is extended.

"When the research has involved subjects who could not give consent and it was not possible to obtain consent from a legally authorized representative, the research usually could not be approved by the IRB because federal regulations did not permit research without consent in most cases," she said.

Synthetic blood

by Nancy Humphrey

Vanderbilt University Medical Center's trauma center is gearing up to test a new synthetic blood product on severely injured patients.

The new product will be administered to patients who are in shock due to excessive blood loss. VUMC is one of 35 health care centers across the country testing the new product to determine if it is a viable alternative to saline infusion, the standard treatment.

The upcoming trial falls under recently adopted federal regulations giving research institutions the authority to treat gravely ill patients with investigational drugs or devices in some emergency situations without their consent (see VUMC Reporter, March 14).

The synthetic blood product, called Diaspirin Cross-Linked Hemoglobin (DCLHb), is a purified human hemoglobin solution. Hemoglobin is the protein in red blood cells that carries oxygen. The synthetic blood product, which has already been proven safe and effective in prior studies, is prepared from units of human red blood cells from volunteer donors who have been tested negative for the viruses that cause hepatitis and AIDS. Unlike blood, it does not need to be cross-matched and is easily stored in the emergency department so that it is available as soon as the patient arrives.

The multi-center study will compare the use of the synthetic blood product to saline, the current standard of treatment when blood is not readily available.

"This study is designed to try to identify the very sickest people who can benefit from the administration of a blood substitute when blood is not available," said Dr. John A. Morris Jr., professor of Surgery, and the principal investigator of the Vanderbilt portion of the study. Also participating in the study will be Judy Jenkins, R.N., M.S.N., clinical nurse specialist and case manager in the division of Trauma.

Before blood can be given to a patient, the patient must be cross-matched so that the correct type of blood is given, Morris explained. Giving a patient the wrong type blood can be a "fatal mistake," Morris said.

Cross-matching can take up to 45 minutes, time that is not available when an injured patient is in shock, he said.

When a patient is in shock the body is unable to deliver enough blood and oxygen to all of the vital organs and tissues, Morris explained. Because of this, the vital organs may no longer be able to function and the patient may die. About 150,000 people die each year due to trauma injuries.

"The ravages of shock are dependent upon two things — the magnitude of the injury and the length of time before the patient gets

therapy for that injury," Morris said. "The most important therapy we can give people is the ability to get oxygen to the tissues," Morris said.

A breathing tube can deliver oxygen from the air to the blood, Morris said. But within the blood there has to be a method by which oxygen is carried to the tissues. That is the importance of hemoglobin.

"In a normal situation, the boxcar that delivers oxygen is called hemoglobin," Morris explained. "Hemoglobin is the business end of what a blood transfusion is all about."

But blood transfusions take time to prepare.

"If we had something to give patients in the first 45 minutes that would carry oxygen, i.e. a boxcar, we could shorten the time they are without enough oxygen to the tissues. And that's good," Morris said.

Currently, when it is not feasible to wait for blood to be given, the treatment of choice is the rapid infusion of large volumes of saline to replace fluid loss due to injury, followed by the transfusion of blood to replace the fluid and blood loss.

The nationwide study will involve approximately 850 severely injured patients at the 35 trauma centers. About 20 to 30 patients will be involved at each institution.

Only those at the greatest risk of death can be considered for the study. Patients can be either male or female and must be at least 18. Patients with severe head injuries or whose heart has stopped in the hospital will not be entered into the study.

The study participants will be randomized. Some will receive the new synthetic blood product. Some will receive an equal amount of saline. The order of assignment will be determined before the patients are entered into the study so neither the patients nor the patients' physician can choose which solution is given.

Morris said the implications of the study are important for several reasons.

"It's important to the people of Tennessee for several reasons. This is a rural state and the transport time to definitive care is relatively long. Consequently the risks of shock are relatively high," he said.

The product may also have military applications.

In the Gulf War, for example, the job of preparing for American casualties of up to 10,000 men was "profound," Morris said.

Blood products, with a shelf life of 30 days, had to be shipped at a point where they wouldn't expire before the hostilities took place.

"It put a significant drain on the civilian blood supply. It was costly. And it was a logistical nightmare," Morris said.

"Imagine the logistics of 10,000 casualties over a week, having to type and cross all of these casualties, needing the logistical support to be able to administer all this blood without killing people by making

mistakes, and doing the whole thing in a combat environment," Morris said.

The new synthetic blood product has a shelf life of more than a year, and can be reconstituted for use after it is frozen.

"All you'd have to do is manufacture it, ship it over on one airplane and reconstitute it when you need it," Morris said. "If this product is proven to work, it may have tremendous implications for the military not far down the road."

Morris said it is believed that the earlier the synthetic blood product is used the better it may work. If the product is proven effective, it will more than likely be of best use before the patients actually get to the hospital, administered while they are en route, either in a ground or air ambulance.

"The next step will be to get this product into the pre-hospital environment," Morris said.

For now, the question of whether the product works better than saline is all that this project attempts to answer.

"It's not a question of whether this product serves as a boxcar. We know it does. It's not a question of whether it's safe. We know it is. The question is can we give it, can we give it early enough and can we give it in volumes sufficient enough to save lives," Morris said.

"We're confident we're not going to make anyone worse. The question is can we make a significant number of people better."

Attachment 16

Vanderbilt University Medical Center Friday, March 14, 1997

cer regimen shows early promise

overall
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cancer — the

drugs 5-fluorouracil (5FU) and leucovorin — with the drug trimetrexate, response rates in patients with unresectable or metastatic rectal cancer improved, said Dr. Charles D. Blanke, assistant professor of Medicine and the study's principal investigator.

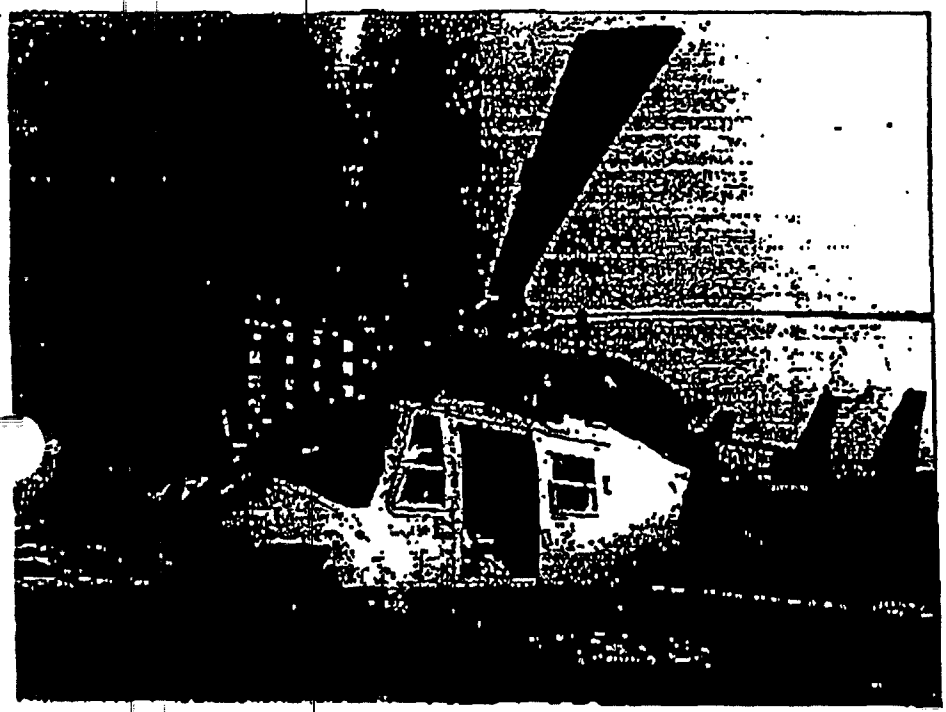
"We observed a 50 percent overall response rate. Also, 7 percent of patients had a complete response, which is a larger number than we expected. These are exciting results," Blanke said.

The results of the phase II trial were recently published in the *Journal of Clinical Oncology*.

The complete responses were seen in patients with disease which had spread only to the liver, but partial responses were seen in all disease sites, Blanke said. The median duration of response was 15.5 weeks. Median

Please see CANCER, page 3

d second helicopter



Donna Marie Jones

d air ambulance service is getting some help with the arrival of a second helicopter.

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nunity," said
associate pro-
irector of the

division of Trauma, and medical director of LifeFlight.

"The new aircraft will be equipped to meet the needs of cardiac patients. Its hours of operation will be designed to maximize the benefit to our referral community for cardiac transports," Morris said.

The new two-aircraft system will be phased in, with a temporary helicopter being used for about six weeks until the permanent aircraft arrives in mid-May. "Eventually what we will be flying is our current aircraft, and the

Please see LIFEFLIGHT, page 2

VUMC set to implement new consent regulations

.....by Doug Campbell

A new federal regulation giving research institutions the authority to treat gravely ill patients with investigational drugs or devices in some emergency situations without their consent is being implemented at Vanderbilt University Medical Center.

The government's guidelines apply to a limited class of research activities — those involving persons in desparate need of possible life-saving treatment but who are unable to give consent and have no family or someone to legally represent them.

"The community-at-large must now be made aware of the specific research being proposed," said Virginia Willey, director of VUMC's Institutional Review Board.

"It's an additional step in the approval process," she said.

Please see CONSENT, page 3

tap

Conference spotlights rapidly changing world of health care

Community involvement is a major component of the week of events. For example, Vanderbilt and the Cumberland Science Museum have joined forces to bring the exhibit "Changing Your Mind: Drugs and the Brain," to Nashville as the first stop on its national tour. The exhibit runs through April 27.

"We would like to have the community learn more about brain research so that they can appreciate the long-term investments that it takes to make major discoveries that impact on mental health and brain diseases," said Blakely.

"Increasingly we have become aware that we need to do more to educate the public about our research objectives.

...will be held in [illegible] Eight Hall at 2:30 p.m. on Friday, Ma... W. Goebel, associate director for Human Subjects Prote... FDA, will speak at the event.

• On Tuesday, March 18, Dr. Steven M. Reppert, Harvard Medical School, will give a lecture entitled "Why Moths Fly at Night: Comparative Analysis of Clock Gene Regulation." The lecture will be held in room 114 Buttrick Hall at 4 p.m.

• A career day for high school students will be held on Wednesday, March 19. Jeanette J. Norden, Ph.D., "O... is to g...

BRAIN

Consent ...

Continued from front page

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...VUMC and Junior Leo... ...brate 25 years of the... ...ed space. Present we... Faust, Peggy Warner,...

Attachment 17

VUMC REPORTER

A medical journal of general interest | Vanderbilt University Medical Center | Friday, April 25, 1997

Trauma center to test synthetic blood product

by Nancy Humphrey

Vanderbilt University Medical Center's trauma center is gearing up to test a new synthetic blood product on severely injured patients.

The new product will be administered to patients who are in shock due to excessive blood loss. VUMC is one of 35 health care centers across the country testing the new product to determine if it is a viable alternative to saline infusion, the standard treatment.

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Please see BLOOD, page 3

Dr. John Morris Jr., talks with nurse Jan Dahlke in the emergency room. Morris is overseeing VUMC's study of a new synthetic blood product.

Donna Marie Jones

NIH study halted early due to defibrillator's effectiveness

by Cynthia Manley

An implantable defibrillator implantable cardiac defibrillators (ICDs) compared with those who had been treated with medica- an ICD in one patient who had been randomized to drug therapy in the trial. We have learned

Cancer Center debuts new 'patient-friendly' chemoinfusion center

by Cynthia Manley

of chemoinfusion chairs to 22. "We feel very fortunate to

Blood ...

Continued from front page

available as soon as the patient arrives.

The multi-center study will compare the use of the synthetic blood product to saline, the current standard of treatment when blood is not readily available.

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"We're confident we're not going to make anyone worse. The question is can we make a significant number of people better." ■

Donna Marie Jones

Caring for kids

Dr. Suzanne Starling, medical director of Our Kids, was recently honored with the Guardian Angel Award from the Exchange Child Abuse Prevention Center for her work evaluating and reported suspected cases of child abuse. Here she accepts the award from Tom Drake, the center's president, during a ceremony on the steps of the Metro Courthouse downtown.

Defibrillator .

Continued from front page

tor was Nancy Conners.

The Antiarrhythmics Defibrillators (AVID) enrolled patients with a his of life-threatening abno heart rhythm involving the tricles, the pumping chambe the heart.

Half the participants h dangerously chaotic rhy called ventricular fibrilla (VF), while the other half h serious ventricular tachyca (VT) — a too-fast heart beat inating from rapid elect impulses in the ventricles.

Of the estimated 350,000 den cardiac deaths that occ the United States each year, are believed to be due to t two conditions. Heart attack cardiomyopathy (heart mu disease) are common cause VF and VT.

In the AVID trial, pati were randomly assigned t treated with either antiarri mic drugs or with an ICD.

An ICD recognizes dange arrhythmias and works to re a normal rhythm by pacing heart or delivering an ele shock. It is implanted ben the skin in the chest an attached to the heart with le

After one year, patients i ICD group experienced a re 38 percent reduction in d compared with the grou patients who were treated medication. In the second third years, the ICD group about a 25 percent reductic deaths.

"Even though the rel benefit for the implantable d rillators compared to d declined over time, the differ between the two treat strategies — even at three — was still very significant," Claude Lenfant, director o National Heart, Lung and B Institute, said in the

Blair String (

All VUMC faculty and sta members are invited to the B String Quartet Brown Bag Concert scheduled for Wednesday, April 30.

Drinks and dessert will be provided at the concert, whi

Attachment 18

The Tennessean

April 30, 1997, Wednesday CITY EDITION
SECTION: NEWS, Pg. 8A

LENGTH: 1212 words

PATIENT'S TRUST IS ESSENTIAL

YOU'VE had a terrible accident. You're losing blood.

You've been rushed to a highly qualified emergency room, which has been federally approved to administer a new blood substitute. But that procedure is still in an experimental phase. Doctors may use it, but it comes without your knowledge or consent.

Is that OK with you?

That's the essence of an issue currently debated over HemAssist, a blood substitute made by Baxter HealthCare Corp. Last fall, the Food and Drug Administration gave 35 medical centers in the nation, including Vanderbilt University Medical Center, the go-ahead to test the substitute on victims of car accidents, gunshot wounds and so forth, without the prior consent of those patients.

Those victims are often in shock not exactly an ideal situation to have a thoughtful question-and-answer session about an experimental substance. And that predicament is why federal authorities have directed participating centers to inform entire communities about the pro- cedure and get input about the plan. Vanderbilt has followed those instructions, alerting local legislators and informing groups such as the Metro Human Relations Commission and Mothers Against Drunk Driving about the plan.

Critics fear that the FDA's relaxation of consent regulations for this substance could signal a move away from strict patient consent.

But the best answer is probably found somewhere in that overwhelming sense of responsibility to inform. Wherever people can be educated, whether it be as an individual patient or the broader population, the medical profession wins trust.

The rules for consent for a substance used almost exclusively in emergency rooms must differ from those used in non-emergency situations.

The FDA rules and Vanderbilt's effort seem to exhibit recognition of the important goal of having an informed public. But sometimes, informed consent of an individual patient is virtually impossible. That's why a push for an informed public must persist.

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